REMARKS

Claims 1-5, 7-8, 11, 12, 14-17, 20-23, 25, 35, 38-40, 45, 48-55, 58, 81, 89 and 91-94 have been amended. Claims 10, 19, 24, 28, 37, 41-43, 80 and 82 have been cancelled. Support for the amendments in the new Claim 1 can be found in: [0055] and [0127] ("amplifying or copying at least one"); [0061] ("primer pairs which are capable of amplifying or copying at least 4 of said target"); [0070] and Claim 28 ("covalently"); [0065] and Claim 19 ("spacer of at least 6.8 nm"); [0150] and Claim 24 ("nucleotide sequence of about 5 to about 60 bases"); [0077], [0142]; [0035], Claim 8 and Claim 37 ("consensus capture nucleotide sequences for a common detection"); [0150] and Claim 10 ("consensus capture nucleotide sequences having a nucleotide sequence length specific of the target comprised between about 10 and about 1000 bases).

Support for the amendments in Claims 4-5, 7-8, 12, 14-16, 35, 39, 48-54, 89 and 91-94 can be found in [0043] ("nucleotide sequences"). Support for the amendment in Claim 89 can be found in [0090] and Example 16.

Support for the amendment in Claim 25 can be found in the now cancelled Claim 24.

Therefore, no new matter has been introduced herewith. The following addresses the substance of the Office Action.

Definiteness

The Examiner has maintained the rejection of Claims 1-8, 10-61 and 80-94 under 35 U.S.C. §112, second paragraph as being allegedly indefinite. More specifically, Claims 1-8, 10-61 and 80-94 have been rejected for reciting "component thereof", which lacks metes and bounds, because the Specification only gives examples what could be encompassed by the recitation of "component", but not specifically what is meant by a "component". Claims 1-8, 10-61 and 80-94 have been rejected for recitation of "characteristic" which does not have a definition in the specification. Claims 1-8, 10-61 and 80-94 have been rejected for lack of antecedent basis for "said nucleotide sequence". Claims 35 and 93 have been rejected for reciting "such as". Claims 37 and 38 have been rejected because it was not clear to the Examiner whether the consensus sequence is attached to the capture sequence or is located separately in a different area of the array than the capture sequence. Claims 91 and 93 have been rejected for improper expression of alternative limitations.

Applicants maintain that the claims were definite, but solely for the purpose of expediting the prosecution of the present application, Applicants have amended the claims to address the

Examiner's concerns. Applicants have amended Claims 1-8, 10-61 and 80-94 by deleting the terms "component thereof", "components" and "characteristic". The deletion of "characteristic" in "nucleotide sequence characteristic" provides the antecedent basis for "said nucleotide sequence". Claims 35 and 93 have been amended by deleting of the term "such as". Claims 91 and 93 have been amended to recite a proper Markush group. Claims 37-38 have been amended to recite "said solid support further comprising a consensus capture nucleotide sequence".

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

Non-obviousness

The Examiner has rejected Claims 1-18, 24-46, 55-61, 80-85 and 87-88 under 35 U.S.C. §103(a) as being allegedly unpatentable over Antony et al. (*J. Clin. Microbiol.* 2000, **38**:781-788) in view of Brown et al (USP 5,807,522). More specifically, the Examiner believes that that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Anthony et al. so as to have included an array comprising at least four different bound single-stranded capture probes/cm^2 of solid support surface of Brown et al., and achieve the benefit of providing a more efficient and more effective means of detecting and discriminating nucleotides sequences form samples of biological organisms by simultaneously analyzing thousands of samples at one time. The applicant respectfully disagrees.

> To establish a *prima facie* case of obviousness, the PTO must cite one or more references that provide some suggestion or motivation to modify the references to achieve the claimed invention, provide a reasonable expectation of success to achieve the claimed invention, and finally, the cited art must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Here, the cited art either taken alone or in combination, fails to provide any of the required factors.

The present invention is related to a method of using arrays comprising covalently bound capture nucleotide sequences wherein these sequences comprise a spacer and a sequence that specifically binds to the target; two categories of capture nucleotides sequences for group and sub-group detection and primer pairs capable of amplifying at least two of 4 homologous sequences. In the presently amended Claim 1, these capture nucleotides sequences are covalently bound to the solid support. In the presently amended claims, the capture nucleotide sequence includes a spacer that places the specific sequence of the capture nucleotide sequence such that it is able to hybridize with the corresponding target nucleotide sequence at a certain distance from

the solid support surface (6.8 nm). In the present invention, as claimed in Claim 1, the binding between the target nucleotide sequence and its corresponding capture nucleotide sequence forms a signal at the expected location (the location of the specific capture nucleotide sequence), the detection of said signal allowing a discrimination of a target sequence from other homologous sequences obtained from other organisms. This means that a single "spot signal" directly allows the identification of a specific organism and that one capture nucleotide sequence is sufficient for the identification of one target nucleotide sequence.

Furthermore, contrary to methods which utilize a pattern of spots, one (single) spot detection allows a precise quantification and thus permits a correlation between intensity of the spot signal and the amount of target nucleotide sequence present. These features are important for improving the sensitivity of the assay.

In contrast to the presently claimed methods in which the capture nucleotide sequences are covalently bound to an insoluble support by a spacer, Anthony et al. teaches the use of short capture probes of 20-25 bases which do not include a spacer. In the method of Anthony et al., the capture probes are immobilized on nylon membranes. The binding of the capture probes on filter or membrane means that there is no control of the part of the sequence which is available for hybridization (Anthony et al. pg. 783, line 2: "The length of the UV exposure used to link the probe on the nylon was found to have a marked effect on the intensity of the resulting spots"). There is no single point attachment of probes on nylon membranes so that the suggestion that the spacer are one key issue of getting specificity and sensitivity could not be proposed nor suggested in Anthony et al. In contrast to the methods of Anthony, the utilization of spacers in the present methods ensures that the portions of the capture nucleotide sequences which are complementary to the target sequences are available for hybridization. Therefore, Anthony in fact teaches away from the present invention as claimed in currently amended Claim 1.

In addition, in the method of Anthony et al. one target sequence can cross-react with several capture probes (note that some of the filters depicted in Fig. 1 of the Anthony reference contain more than one position of hybridization). In such cases, it is the pattern of several positive spots which allows specific identification of the organism present. This means that the interpretation of the result is not straightforward.

In addition, Anthony et al.'s array does not comprise two categories of capture nucleotide sequences for group (e.g., genus) and sub-group (e.g., species) simultaneous detection as recited

in the present claims. The probes listed in Table 2 of Anthony et al. are asserted to be specific for a single bacteria species except one that represents a genus (Listeria spp.). Thus, there is no teaching or suggestion in Anthony et al. of using both a capture nucleotide sequence for the genus and a capture nucleotide sequence specific to the species. Thus, the methods of Anthony do not permit simultaneous identification and quantification of groups and subgroup of bacteria as is possible with the present arrays.

Combination of documents

Anthony et al. provides no motivation to utilize the disclosed methodology with an array comprising at least 4 different bound single-stranded capture molecule probes/cm^2 of solid support surface as allegedly described by Brown et al. In fact, this combination would not lead to a method for efficiently detecting target sequences, especially target sequences belonging to groups, and sub-groups of organisms.

In contrast to the claimed methods in which the single-stranded capture nucleotide sequences are covalently bound to an insoluble support via a spacer, Brown teaches the use of capture probes non-covalently immobilized on polylysine coated on the surface of glass slides. Therefore, this document, in fact, also teaches away from the present invention as claimed. In addition, in the method of Brown, the capture probes are immobilized on polylysine coated on the surface of glass slides. In such method, there is no control of which portion of the probe is available for hybridization. Such method is not desirable for the discrimination between closely related sequences as was also noted in the Anthony et al. publication.

Furthermore, the inventors completed the invention of this application prior to February 2000, the date that appears on Antony et al. publication, and therefore the cited reference does not constitute prior art. The Declaration under 37 CFR §1.131 supporting this assertion will be submitted shortly.

Therefore, the combination of Anthony et al. and Brown et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 1-18, 24-46, 55-61, 80-85 and 87-88 under 35 U.S.C. §103(a) is respectfully requested.

The Examiner has rejected Claims 19-23 and 87 under 35 U.S.C. §103(a) as being allegedly unpatentable over Antony et al. (*J. Clin. Microbiol.* 2000, **38**:781-788) in view of Brown et al. (USP 5,807,522) as applied to Claims 1-18, 24-46, 55-61, 80-85 and 87-88 above, and further in view of Bamdad (USP 6,541,617). More specifically, the Examiner alleges that in

view of the teaching of Anthony et al. it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Anthony et al. so as to have included a spacer as described by Brown et al. in order to achieve the benefit of the invention and to have further modified the method of Anthony et al. so as to have used a spacer of at least 6.8 nm, in order to achieve the benefits stated by Bamdad et al. (i.e. increasing the kinetics of hybridization), thus providing a more efficient means of hybridization / detection. The applicant respectfully disagrees.

The irrelevance of teachings of Anthony and Brown to the present invention is discussed above. Bamdad et al. teaches the use of colloid particles comprising ligands and electron transfer moieties (ETM) for covalent binding of target analyte to an electrode surface. Bamdad et al. teaches that for efficient hybridization of nucleic acids on a surface, the hybridization should occur at a distance from the surface. However, this document also teaches that a spacer between 15 and 60 Å and up to 500 Å long for positioning a nucleic acid on a surface is particularly important for long double-stranded oligonucleotides of 200 to 300 base pairs. Therefore, based on the teaching of Bamdad et al., it would not have been obvious for an ordinary skilled person to use a spacer of 6.8 nm long for positioning of short sequences comprising 5-60 bases of single-stranded DNA.

Therefore, the combination of Anthony et al., Brown et al. and Bamdad et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 19-23 and 87 under 35 U.S.C. §103(a) is respectfully requested.

The Examiner has rejected Claims 43, 48-54, 86, and 89-94 under 35 U.S.C. §103(a) as being allegedly unpatentable over Antony et al. (*J. Clin. Microbiol.* 2000, **38**:781-788) in view of Brown et al. (USP 5,807,522) as applied to Claims 1-18, 24-46, 55-61, 80-85 and 87-88 above, and further in view of: Gingeras (USP 6,228,575) - Claim 43; Boon et al. (USP 6,488,932) - Claim 48; Apple et al. (USP 5,451,512) - Claim 49; Klein et al. (USP 6,255,059) - Claims 50, 51, and 53; Murphy et al. (WO 94/05695) - Claim 52; Waxman et al. (USP 6,207,648) - Claims 54 and 90; Vannuffel et al. (WO 99/16780) - Claim 86; Musser (Clin. Microbiol. Rev. 1995 8:496-514) - Claim 89; Rose et al. (Nuc. Acid Res. 1998 26:1628-1635) - Claims 91 and 93; Apostolidis et al. (Heredity 1996 77:608-618, abstract only) - Claim 92; and Dickinson et al. (US 2002/0102578) - Claim 94. More specifically, the Examiner believes that because these additional references describe specific sequences belonging to a Microbacteria family, MAGE

family, HLA-A family, G gene family, cytochrome P450 isoforms family, dopamine or histamine receptors coupled to the G gene family, FemA gene of staphylococci species family, A gyrase family, sequences belonging to specific animal species or sequences belonging to genetically modified organisms, it would have been obvious to combine these refences with the teachings of Antony et al., and Brown et al. Applicant respectfully disagrees.

The additional references fail to cure the primary references' lack of teaching or suggestion of the characteristics of the method according to the present invention as discussed above. Therefore, Applicant asserts that Claims 43, 48-54, 86, and 89-94 are non-obvious in view of the cited prior art, and respectfully requests withdrawal of their rejection under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing, Applicants respectfully submit the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 18, 2005

By: _____

Marina L. Gordey
Registration No. 52,950
Agent of Record
Customer No. 20,995
(805) 547-5580

1817911
071505